Neuropharmacology
Part 1

1st ISBS Summer School

St. Petersburg, Russia

May 9th -15th,2008

Antidepressant drugs

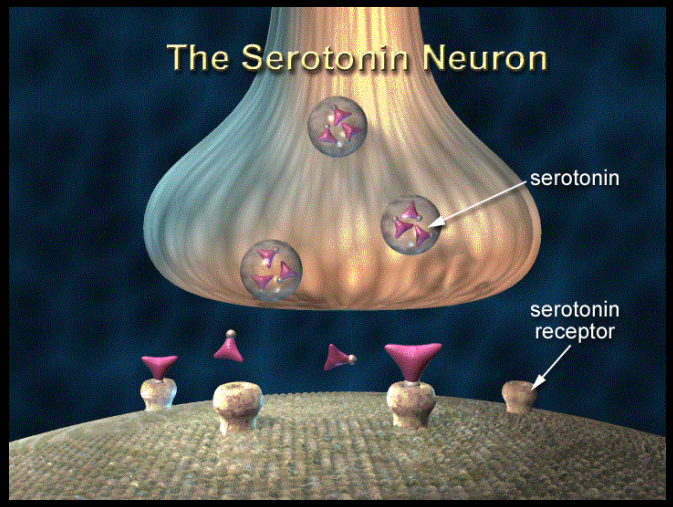
Selective serotonin reuptake inhibitors (SSRIs)

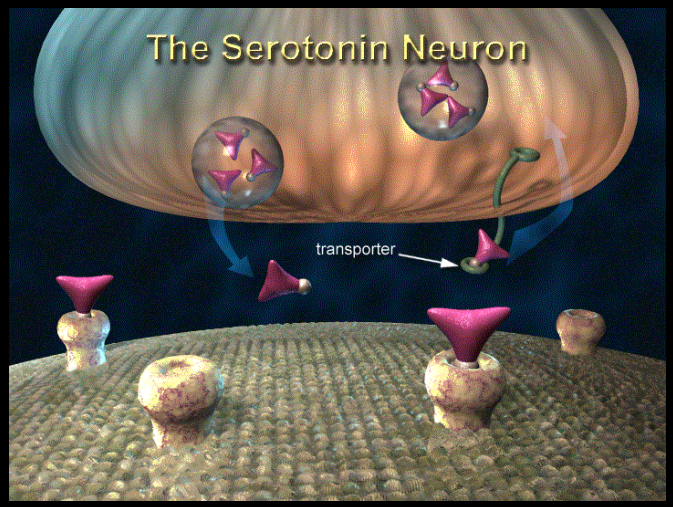
- citalopram (Celexa, Cipramil, Emocal, Sepram, Seropram)
- escitalopram oxalate (Lexapro, Cipralex, Esertia)
- fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR))
- fluvoxamine maleate (Luvox, Faverin)
- paroxetine (Paxil, Seroxat, Aropax, Deroxat, Rexetin, Xetanor, Paroxat)
- sertraline (Zoloft, Lustral, Serlain)
- Dapoxetine

Monoamine Oxidase Inhibitors (MAOI's)

- Isocarboxazid *(Marplan)*
- Moclobemide *(Aurorix, Manerix, Moclodura®)*
- Phenelzine *(Nardil)*
- Rasagiline *(Azilect)*
- Nialamide
- Iproclozide
- Toloxatone
- Tranylcypromine

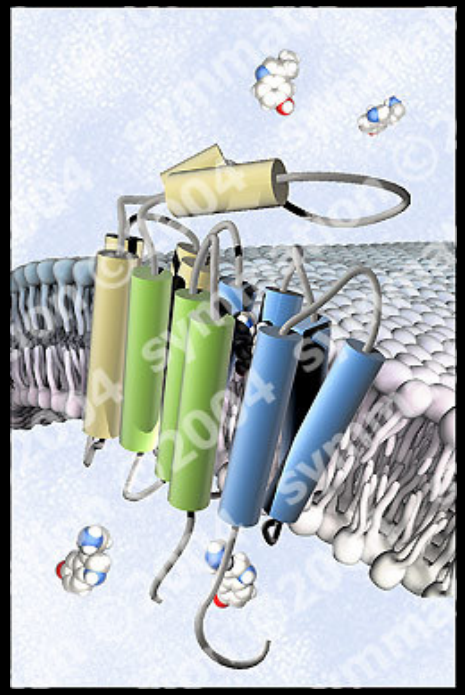
SSRIs and SERT





Serotonin transporter (SERT) is the key regulator of serotonergic neurotransmission

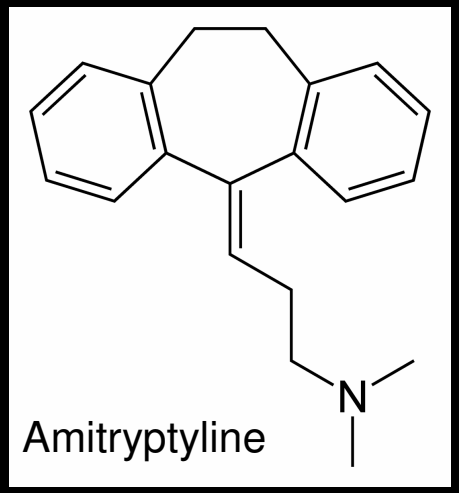
SERT is a target of many psychotropic drugs [SSRIs]



Antidepressant drugs

Tricyclics

- Amitriptyline *(Elavil, Endep, Tryptanol, Trepiline)*
- Amoxapine *(Asendin, Asendis, Demolox, Moxadil)*
- Clomipramine *(Anafranil)*
- Desipramine *(Norpramin, Pertofrane)*
- dothiepin hydrochloride *(Prothiaden, Thaden)*
- lofepramine (Gamanil)
- Nortriptyline (Pamelor)
- Opipramol (Opipramol-neuraxpharm, Insidon)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)



Amitryptyline

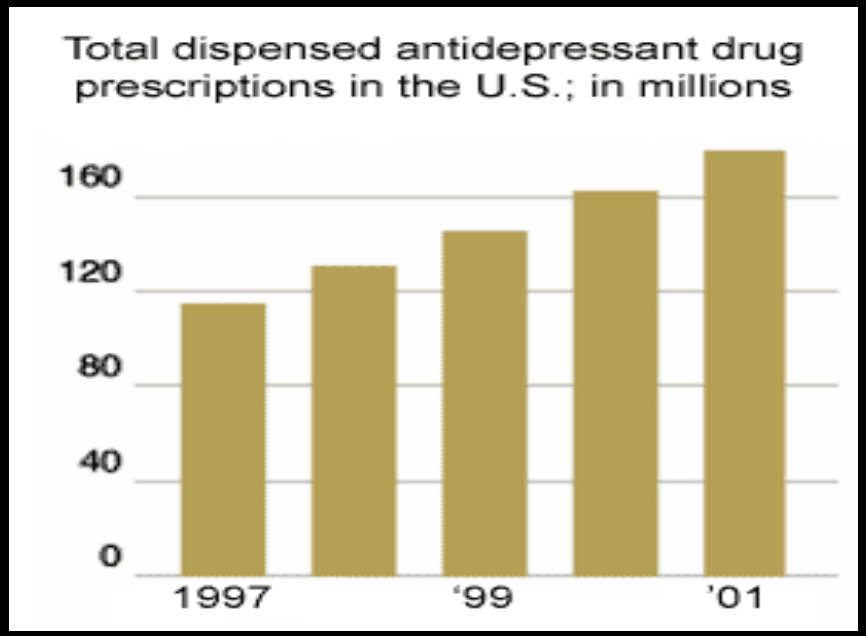
Herbs and nutrients

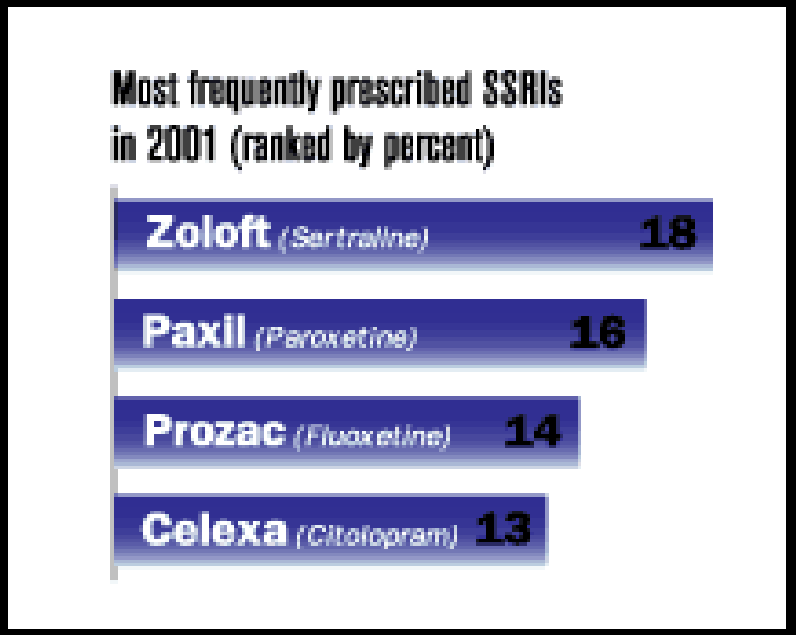
- St John's Wart
- Phenylalanine
- tyrosine
- tryptophan
- 5-Hydroxytryptophan
- choline


St John's Wart

Antidepressant use on the rise

- Adult use of antidepressants tripled between the periods 1988-1994 and 1999-2000
- Of the 2.4 billion drugs prescribed in 2005, 118 million were for antidepressants

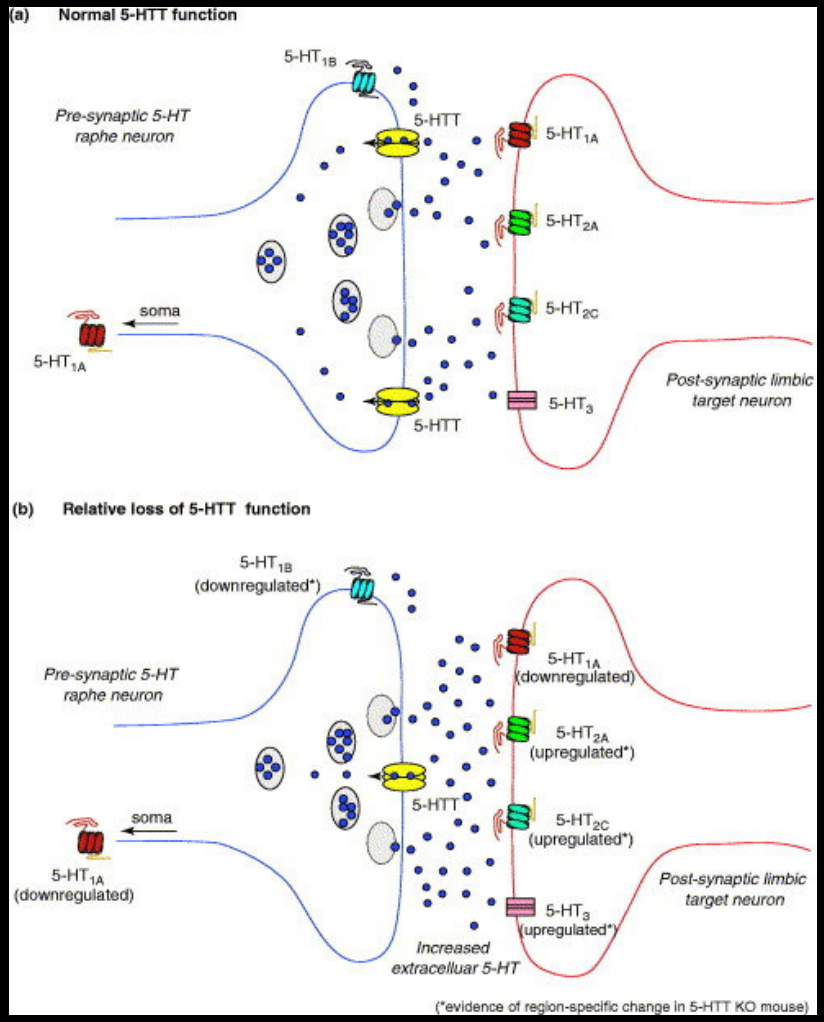




Side effects of antidepressants

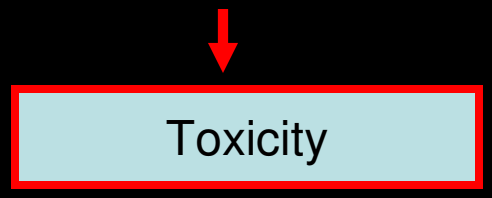
- Dry mouth
- Urinary retention
- Blurred vision
- Constipation
- Sedation
- Sleep disruption
- Weight gain
  Headache
- Anxiety
- Nausea
- Gastrointestinal disturbance/diarrhea
- Abdominal pain
- Sexual dysfunction
- Agitation
- Suicides
- Serotonin toxicity

SSRIs, SERT and SS



Normal brain serotonin

Excess of brain serotonin



Serotonin toxicity

A disorder caused by exaggerated serotonergic function in the brain, most commonly after antidepressant overdose or after combining several psychotropic medications

Similar condition (serotonin syndrome-like behavior) can be evoked in animals experimentally, following administration of serotonergic drugs

Genetic and other factors may also contribute to serotonin toxicity

Genetic animal models of serotonin toxicity

- Some animals display spontaneous SS-like phenotype, while other animals may show hypersensitivity to drugs that induce SS-like behaviors, or both
- SERT knockout (–/–) mice are a useful tool to assess the role of serotonin and SERT in various brain disorders These mice display increased extracellular serotonin, altered expression of several serotonin receptors, and numerous behavioral anomalies, including hypolocomotion and anxiety
- SERT–/– mice spontaneously display Straub tail, tremor, tics, hind leg abduction, backward gait and flat back/low posture

Kalueff et al., 2007

Genetic animal models of serotonin toxicity

- SERT–/– mice: 10-fold increase in serotonin
- Baseline hyperthermia has been reported
- Exaggerated SS-like behaviors are found in SERT–/– versus SERT+/+ mice treated with serotonin-enhancing drugs
- Heterozygous SERT+/– mice display hypersensitivity to SSRIs and are highly relevant to human SERT genetic polymorphisms
- SERT+/– mice are characterized by multiple dysregulation in serotonergic systems and display exaggerated drug-induced SS-like responses

Kalueff et al., 2007; Fox et al., 2008

Neuroleptic malignant syndrome

A life-threatening idiosyncratic reaction characterized by muscle rigidity and hyperthermia, related to acute dopamine depletion, either from the use of neuroleptic drugs or of dopamine antagonists, or the withdrawal of dopamine agonists

SS vs NMS: fast vs slow

http://www.intox.org/databank

Neuroleptic malignant syndrome

- Extreme hyperpyrexia,
- lead-pipe muscular rigidity,
- autonomic dysfunction (tachycardia, elevated or fluctuating blood pressure)
- sweating
- respiratory failure
- altered mental status (confusion, delirium, stupor and coma),
- Acute renal failure may occur
- Fatal in up to 12 % of cases

http://www.intox.org/databank

Malignant hyperthermia (MH)

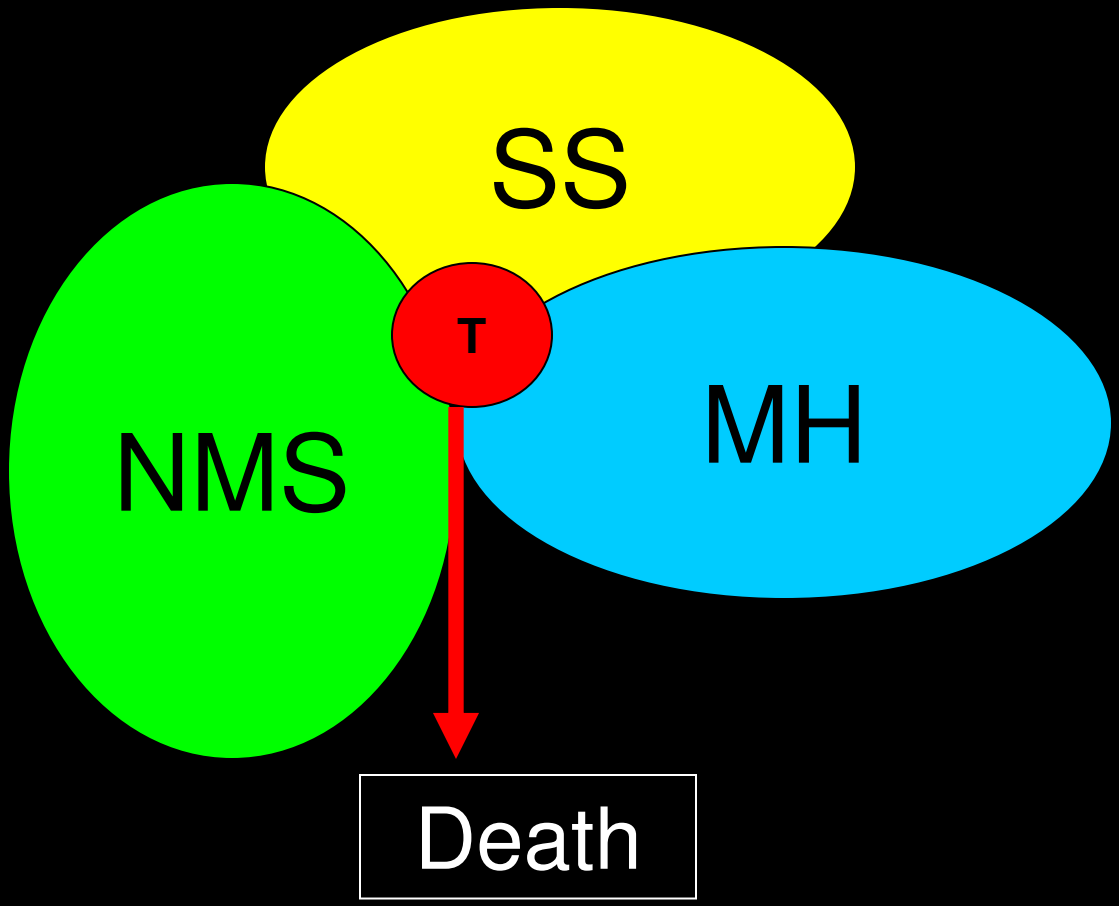
- Pharmacogenetic disease of skeletal muscle
- When exposed to inhalational anesthetics, muscle metabolism increases, and a series of signs and symptoms appear, which if left untreated can lead to death
- The earliest findings are an increased production of carbon dioxide and signs of increased sympathetic nervous system activity

Malignant hyperthermia (MH)

Clinical symptoms:

- hypermetabolism (↑ O2 consumption, CO2 production)
- muscle rigidity
- muscle injury
- increased sympathetic nervous system activity
- increase in body temperature

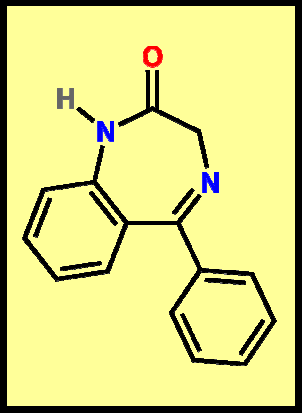
Neurotoxic syndromes: similar, but different



Anxiolytic treatments

Pharmaceuticals
SSRIs

- fluoxetine (*Prozac*)
- paroxetine (*Paxil*)
- escitalopram (*Lexapro*)



Core chemical structure of benzodiazepines

Benzodiazepines

- alprazolam (*Xanax*)
- chlordiazepoxide (*Librium*)
- clonazepam (*Klonopin*)
- diazepam (*Valium*)
- lorazepam (*Ativan*)

Kava plant

Herbal

- Kava (relaxant made from the root of Kava plant)

Hallucinogens: Acid trip (LSD)

20 min

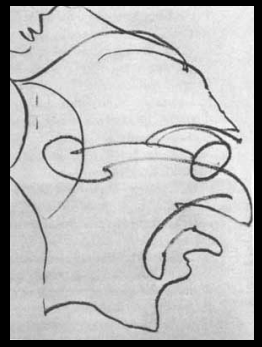
"… I'm having a little trouble controlling this pencil. It seems to want to keep going…"

1 h 25 min

2 h 30 min

"… everything is changing color… Everywhere…" Patient becomes startled by something on the floor

2 h 32 min



2 h 35 min

Patient is generally agitated, and becomes largely none-verbal. "I am... everything is... changed... they're calling... your face... interwoven... who is..." Patient mumbles…

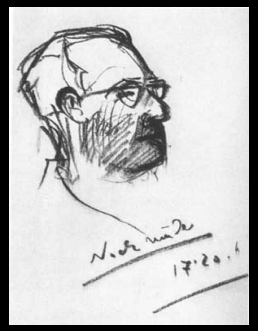
2 h 45 min

4 h 25 min

Running back and forth across the room

5 h 45 min

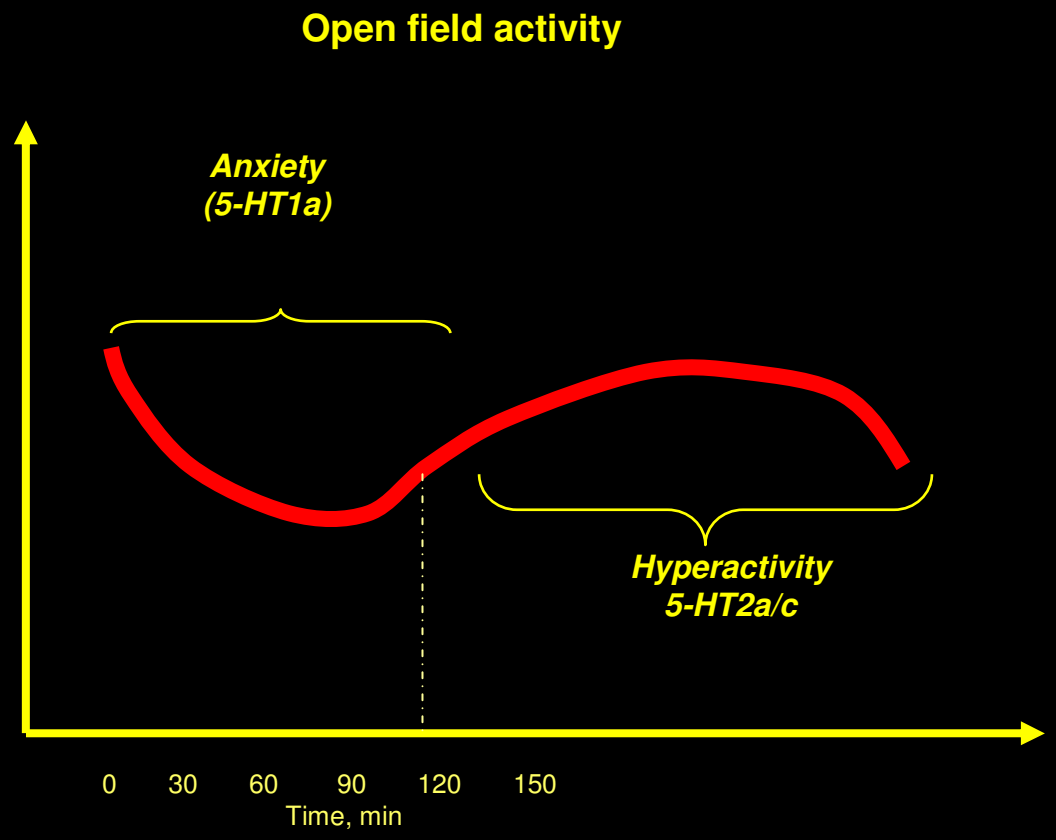
"…I can feel my knees again…"



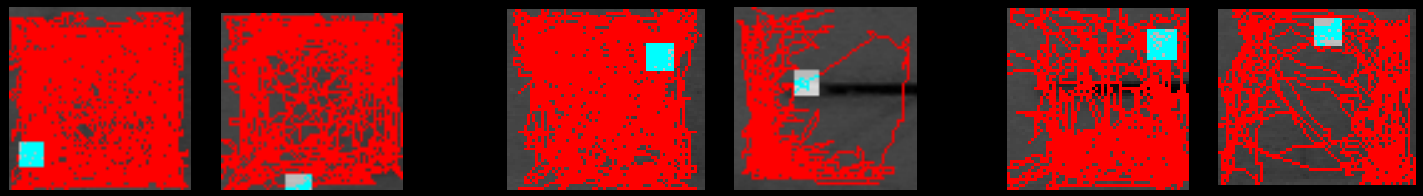
8 h 00 min

Patient sits on his bed. He reports that intoxication has worn off except for the occasional distorting of faces

Behavioral effects of LSD in rodents



LSD and SERT-/- mice: potential clinical relevance to substance abuse phenotypes



SERT-/- mice are insensitive to LSD anxiogenic phase of action (likely due to down-regulation of 5-HT1a receptors)

SERT+/- mice appear to be hypersensitive to LSD, suggesting higher sensitivity to hallucinogenic drugs and other drugs of abuse

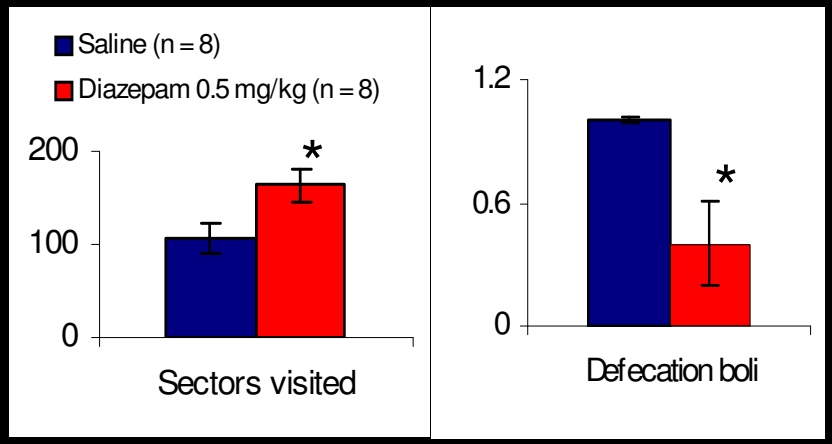
Kalueff et al., 2008

These findings are consistent with mounting clinical data showing association of s/s and s/l genotypes with increased drug abuse phenotype and alcoholism

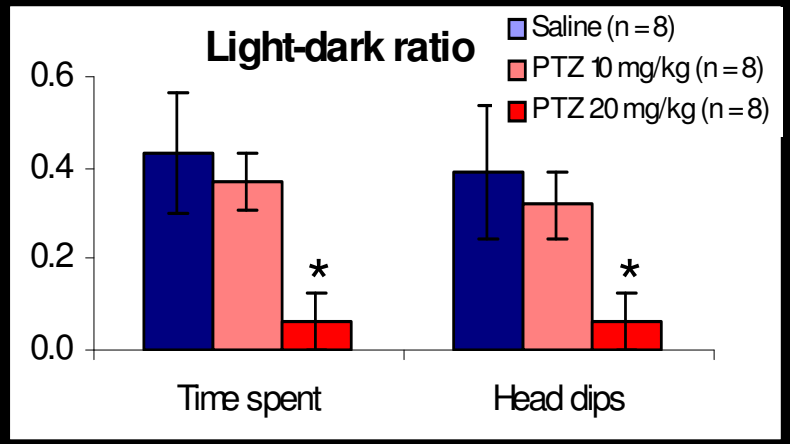
Mice with reduced SERT function may lead to genetic models of these disorders

Suok Test pharmacology

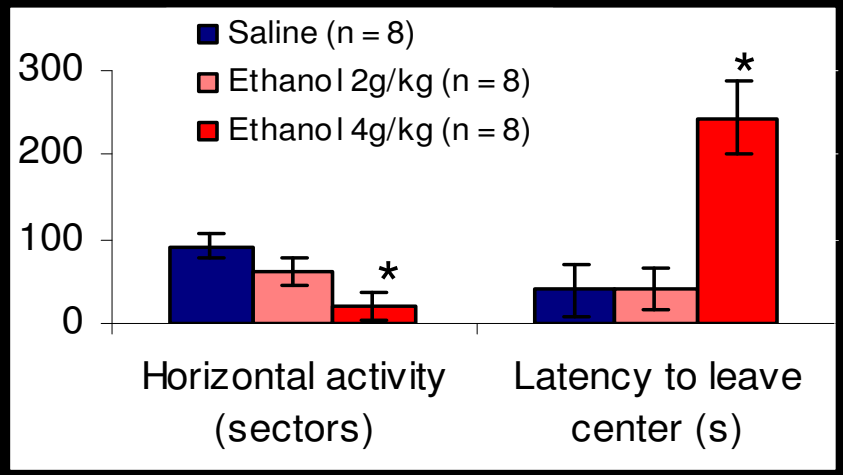
Regular BALB/c mice



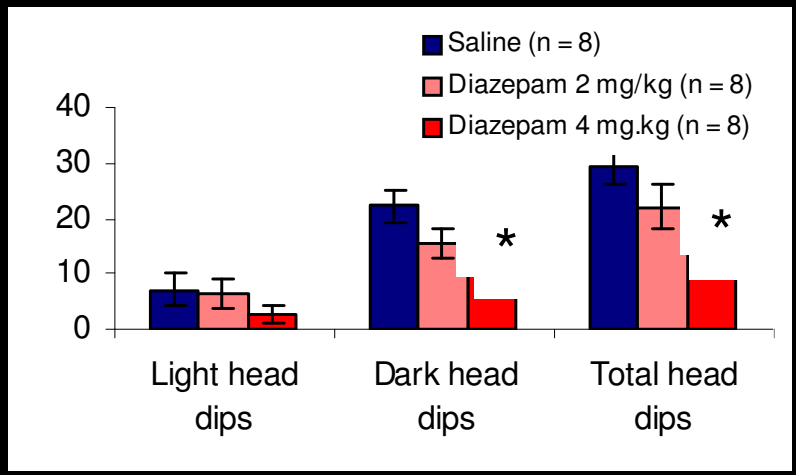
Light/dark BALB/c mice



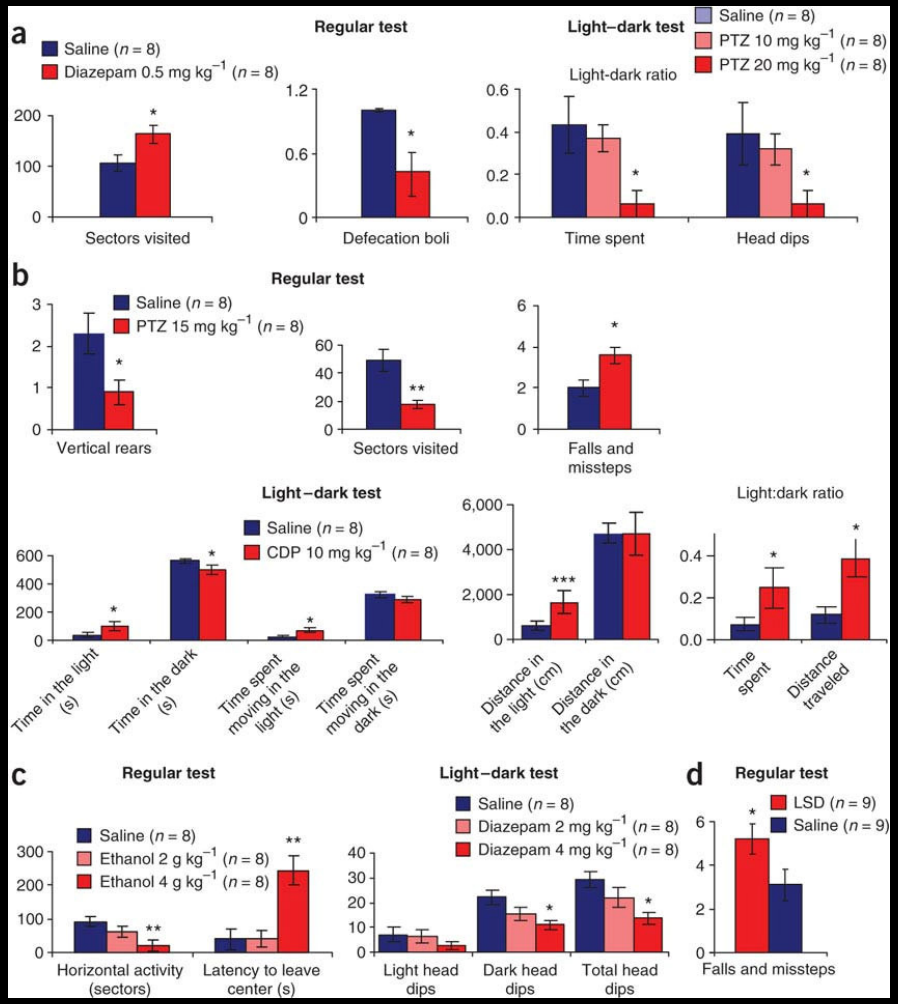
129S1 mice



129S1 mice



The Suok test of anxiety and balancing

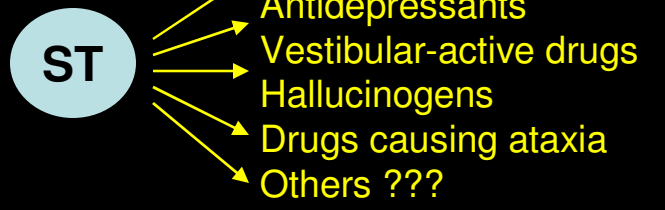


Kalueff et al., 2008, Nature Protocols

Accessibility and advantages:

- High-throughput test
- Simultaneously assess 2+ domains
- Short, efficient trials
- Simple, inexpensive apparatus
- No animal training required
- Combines principles of 4 major tests

Sensitivity to several classes of drugs



Other pharmacological responses for high-throughput testing

Alcohol - locomotion/exploration baseline startle amplitude
Amphetamine - locomotion/exploration
Cocaine - locomotion/ exploration, hot plate test
MDMA - locomotion exploration
Desipramine - forced swim test,
Paroxetine - tail suspension test
Haloperidol - locomotion/exploration, catalepsy, temperature
Clozapine – locomotion/exploration, temperature
Midazolam – thigmotaxis in open field
A-carboline – thigmotaxis in open field
Scopolamine – locomotion/exploration

NIMH, 2000

AS YOU CAN SEE FROM HIS VIOLENT RESISTANCE TO BEING FORCIBLY INJECTED WITH A COCKTAIL OF PSYCHOTROPIC DRUGS THE PATIENT IS CLEARLY PSYCHOTIC!